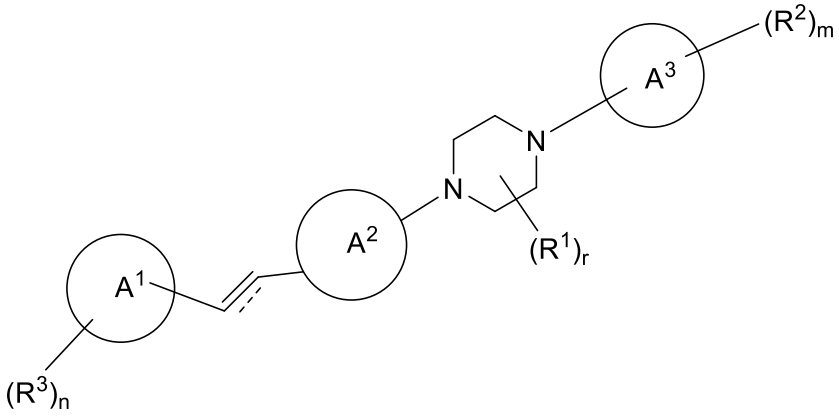
diagnosis of neurodegenerative diseases characterized by alpha-synuclein pathology. The invention further relates to a method of measuring clinical efficacy of therapeutic agents targeting alpha-synuclein pathology.

SUMMARY

[0008] The disclosure is directed to compounds of Formula I, pharmaceutical salts thereof, pharmaceutical compositions comprising them, diagnostic and therapeutic uses and processes for making such compounds. The disclosure, in one aspect, provides a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof wherein;

-------- may be absent or may represent a bond;

R is independently selected from H or $–C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^a is independently selected from H, $–C_{1-6}$alkyl, $-(CH_2)_pOR$, $-(CH_2)_p$halo, or $-(CH_2)_pO(CH_2)_p$halo;

R^b is independently selected from H, $–C_{1-6}$alkyl, heterocyclyl, heteroaryl, $-(CH_2)_sOR$, -CN, $-(CH_2)_t$halo, $-(CH_2)_sNR_2$ or $-O(CH_2)_p$halo;

R^c is independently selected from H, halo, OR, or $–C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^1 is selected from $-(CH_2)_sOR$, $-(CH_2)_sNR_2$, $-(CH_2)_s[O(R^c{}_2)_p]_x-R^c$, or $-(CH_2)_s$halo;

R^2 is independently selected from H, OR, CN, halo or $-C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^3 is independently selected from $-C_{1-6}$alkyl, heteroaryl or heterocyclyl, wherein said alkyl, heteroaryl or heterocyclyl is optionally substituted with one to three groups from OR^a or R^b;
Ring A^1 is selected from pyridinyl, imidazo-pyrimidinyl, triazinyl, pyrimidinyl, imidazo-pyridinyl, pyrazinyl or pyridazinyl;
Ring A^2 is selected from pyrimidinyl, pyridinyl, pyrazinyl or phenyl, wherein said pyrimidinyl, pyridinyl, pyrazinyl or phenyl is optionally substituted with one to three groups from $-C_{1-6}$alkyl, OR^a or halo;
Ring A^3 is selected from pyridinyl, pyrazinyl, pyrimidinyl, pyrrolopyrazinyl, triazinyl, indolyl, imidazolyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, 3,4-dihydro-2H-pyrido[3,2,b][1,4]oxazine or phenyl;
m is selected from 0, 1, or 2;
n is selected from 1, 2, or 3;
p is independently selected from 1, 2 or 3;
r is selected from 1, 2 or 3;
s is independently selected from 0, 1, 2, 3, 4, 5 or 6;
t is independently selected from 0, 1, 2, 3, 4, 5 or 6; and
x is independently selected from 1, 2, 3, 4, 5 or 6.

[0008a] The disclosure, in another aspect, provides a compound selected from

Ex No.	**Chemical Name**
1	(*R,E*)-(4-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-1-(pyrimidin-2-yl)piperazin-2-yl)methanol;
2	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
3	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
4	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(3-((fluoromethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
5	(*R,E*)-5-(2-(6-(4H-1,2,4-triazol-4-yl)pyridin-3-yl)vinyl)-2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidine;

6	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-((2-methoxyethoxy)methyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidine;
7	(*R,E*)-(2-(4-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)methanol;
8	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(5-(fluoromethyl)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine;
9	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-(methoxymethyl)-4-(5-(methoxymethyl)pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
10	(R)-(4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-1-(pyrimidin-2-yl)piperazin-2-yl)methanol;
11	(R)-5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
12	(R)-5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)-2-(4-(6-fluoropyrimidin-4-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine;
13	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(6-fluoropyrimidin-4-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine;
14	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(6-chloropyrimidin-4-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine;
15	(*R,E*)-(1-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-4-(6-fluoropyrimidin-4-yl)piperazin-2-yl)methanol;
16	(*R,E*)-4-(5-(2-(2-(4-(4-fluoropyridin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)morpholine;
17	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(4-fluoropyridin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine;
18	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidine;
19	(*R,E*)-6-(2-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)-2-methylimidazo[1,2-a]pyrimidine;
20	(*R,E*)-2-(5-(2-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole;

21	(*R,E*)-7-(4-(5-(2-(6-(1H-pyrazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrrolo[1,2-a]pyrazine;
22	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(3-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidine;
23	(*R,E*)-(1-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-4-(pyrazin-2-yl)piperazin-2-yl)methanol;
24	(*R,E*)-(1-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-4-(pyrimidin-4-yl)piperazin-2-yl)methanol;
25	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-(methoxymethyl)-4-(5-methylpyrimidin-2-yl)piperazin-1-yl)pyrimidine;
26	(*R,E*)-5-(5-(2-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole;
27	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(5-fluoropyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine;
28	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
29	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(2-fluoropyridin-4-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine;
30	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
31	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-((2-fluoroethoxy)methyl)-4-(pyridin-4-yl)piperazin-1-yl)pyrimidine;
32	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(6-fluoropyridin-3-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine;
33	(*R,E*)-(1-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-4-(6-fluoropyridin-3-yl)piperazin-2-yl)methanol;
34	(*R,E*)-4-(4-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-2-fluoropyrimidine; and
35	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(5-(2-fluoroethoxy)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine;
36	(R,E)-5-(5-(2-(2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole

37	(R,E)-5-(2-(6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-3-yl)vinyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine
38	(R,E)-5-(5-(2-(2-(3-((2-(2-fluoroethoxy)ethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole
39	1-((2-((R)-4-(5-((E)-2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)-3-fluoropropan-2-ol
40	(R,E)-2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-(2-(6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidine
41	(R,E)-5-(5-(2-(2-(3-((2-fluoroethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole
42	(R,E)-5-(5-(2-(2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-4-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole
43	(R,E)-2-(2-((2-fluoroethoxy)methyl)-4-(5-(2-(2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)vinyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
44	(R)-2-(2-((2-fluoroethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
45	(R)-5-((6-(4H-1,2,4-triazol-4-yl)pyridin-3-yl)ethynyl)-2-(4-(6-fluoropyrimidin-4-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine
46	(R)-2-(4-(5-((2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
47	(R)-2-(4-(5-((6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
48	(R)-5-(5-((2-(3-((2-(2-fluoroethoxy)ethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)oxazole
49	(R)-2-(2-((2-fluoroethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-3-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
50	(R)-2-(2-((2-fluoroethoxy)methyl)-4-(5-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
51	(R)-2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine
52	(R)-2-(3-((2-(2-fluoroethoxy)ethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine

53	(R)-2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-4-yl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine
54	(R)-2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-5-((2-(3-(methoxymethyl)-4-(pyrimidin-4-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyrimidine
55	(R)-5-(5-((2-(3-((2-fluoroethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)oxazole
56	(R)-2-(4-(5-((2-(1-(fluoromethyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
57	(R)-2-(4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)-6-fluoropyrazin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine
58	(R)-5-((6-(4H-1,2,4-triazol-4-yl)pyridin-3-yl)ethynyl)-4-fluoro-2-(3-(methoxymethyl)-4-(pyrimidin-4-yl)piperazin-1-yl)pyrimidine
59	(R)-5-((6-(3-fluoro-4H-1,2,4-triazol-4-yl)pyridin-3-yl)ethynyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine
60	(R)-2-(4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-4-fluoropyrimidine
61	(R)-4-(4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-2-fluoropyrimidine
62	(S)-5-(5-((2-(3-((2-fluoroethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)oxazole
63	3-(((R)-4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-1-(pyrimidin-2-yl)piperazin-2-yl)methoxy)-2-fluoropropan-1-ol
64	(R)-5-(5-((2-(4-(2-fluoropyridin-4-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)oxazole
65	1-(4-(6-fluoropyrimidin-4-yl)-1-(5-((6-(oxazol-5-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)piperazin-2-yl)-N-methylmethanamine
66	(R)-5-(5-((2-(4-(5-(2-fluoroethoxy)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)oxazole
67	1-fluoro-3-(((R)-4-(5-((6-(oxazol-5-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-1-(1,3,5-triazin-2-yl)piperazin-2-yl)methoxy)propan-2-ol
68	(R)-5-((6-(3-fluoroazetidin-1-yl)pyridin-3-yl)ethynyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine

69	(R)-5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)-2-(4-(6-fluoropyrazin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine
70	(R)-2-(4-(5-((6-(4H-1,2,4-triazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-((2-fluoroethoxy)methyl)piperazin-1-yl)-1,3,5-triazine
71	(R)-5-((6-(4H-1,2,4-triazol-4-yl)pyridin-3-yl)ethynyl)-2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine
72	5-((6-((S)-3-fluoropyrrolidin-1-yl)pyridin-3-yl)ethynyl)-2-((R)-3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine
73	(R)-1-(5-((2-(3-((2-fluoroethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-1H-pyrazol-4-amine
74	(R)-5-(5-((2-(3-((3-fluoropropoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)oxazole
75	(R)-7-(5-((2-(3-((2-fluoroethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine
76	(R)-5-((6-(4-(2H-1,2,3-triazol-2-yl)piperidin-1-yl)pyridin-3-yl)ethynyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine
77	(R)-2-(4-(5-((6-(1-(2-(2-fluoroethoxy)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
78	(R)-2-(2-((2-(2-fluoroethoxy)ethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
79	(R)-5-((2-(3-((2-(2-fluoroethoxy)ethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)-2,5'-bipyrimidine
80	(R)-2-(4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)-4-fluoropyrimidin-2-yl)-2-((2-methoxyethoxy)methyl)piperazin-1-yl)-1,3,5-triazine
81	(R)-2-(4-(5-((6-(6-fluoropyrimidin-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine-5-carbonitrile
82	(R)-2-(3-((2-(2-(2-fluoroethoxy)ethoxy)ethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine
83	(R)-2-(3-(13-fluoro-2,5,8,11-tetraoxatridecyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine

84	(R)-2-(4-(5-((2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
85	(R)-2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-5-((2-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyrimidine
86	(S)-5-((2-(4H-1,2,4-triazol-4-yl)pyrimidin-5-yl)ethynyl)-2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidine
87	(S)-2-(4-(5-((2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
88	(R)-5-fluoro-2-(4-(5-((2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine
89	(R)-5-((2-(4H-1,2,4-triazol-4-yl)pyrimidin-5-yl)ethynyl)-2-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine
90	(R)-5-fluoro-2-(4-(5-((6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine
91	(R)-2-(4-(5-((2-(1-(3-fluoropropyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
92	(R)-5-(2-fluoroethoxy)-2-(2-(methoxymethyl)-4-(5-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)pyrimidine
93	(R)-5-(5-((2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)oxazole
94	(R)-2-(4-(6-fluoropyrimidin-4-yl)-3-(methoxymethyl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine
95	(R)-2-(2-((fluoromethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
96	(S)-2-(3-((2-fluoroethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
97	(R)-5-fluoro-2-(2-((2-fluoroethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-3-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)pyrimidine
98	(R)-2-(2-((2-fluoroethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-5-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine

or a pharmaceutically acceptable salt thereof.

[0009] The present disclosure is also directed to isotopically-labeled compounds of Formula I. Additionally, the present disclosure provides pharmaceutical compositions

comprising a compound of Formula I and at least one pharmaceutically acceptable carrier. The disclosure, in another aspect, provides a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutical excipient.

[0010] The present disclosure is directed to compounds of Formula I which may be useful for binding alpha-synuclein aggregated proteins and/or tau aggregated proteins, and hence are useful in binding and imaging alpha-synuclein aggregated protein pathology in PD and non-PD synucleinopathy patients as well as aggregated Tau protein pathology Alzheimer's Disease (AD) and non-AD tauopathy patients via PET imaging techniques known commonly in the field (see *J. Nucl. Med.* 2019, *60*, 93-99 and 107-114). This disclosure also relates to methods of using compounds of Formula I to identify patients with abnormal levels of aggregated alpha-synuclein pathology in the brain. This disclosure also relates to methods of using a compound of Formula I as a to measure progression of alpha-synuclein pathology over time as a biomarker in clinical assessment of potential therapeutic agents that can modify Parkinson's Disease progression.

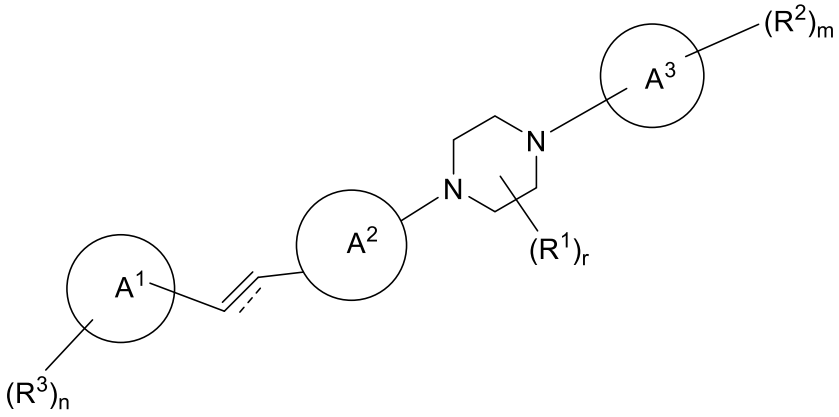
[0010a] The disclosure, in another aspect, provides a method of measuring the clinical efficacy of therapeutic agents for Parkinson's disease comprising the steps of a) measuring the amount of alpha-synuclein aggregate formation in a patient's brain tissue after administration of an isotopically-labeled compound of Formula I, as defined herein, wherein the patient is one diagnosed with PD and before treatment with said therapeutic agent, b) measuring the amount of alpha-synuclein aggregate formation in the patient's brain tissue after administration of an isotopically-labeled compound of Formula I, as defined herein and after treatment with said therapeutic agent, and c) analyzing whether said therapeutic agent stopped or decreased the progression of alpha-synuclein aggregate formation in the patient's brain tissue.

[0011] Compounds of this disclosure may also be useful for imaging and detecting for other neurodegenerative diseases characterized by the deposition of alpha-synuclein aggregates such as multiple system atrophy (MSA) and dementia with Lewy Bodies (DLB).

[0011a] The disclosure, in another aspect, provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use as an imaging agent.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof wherein;

-------- may be absent or may represent a bond;

R is independently selected from H or $–C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^a is independently selected from H, $–C_{1-6}$alkyl, $-(CH_2)_pOR$, $-(CH_2)_p$halo, or $-(CH_2)_pO(CH_2)_p$halo;

R^b is independently selected from H, $–C_{1-6}$alkyl, heterocyclyl, heteroaryl, $-(CH_2)_pOR$, -CN, $-(CH_2)_t$halo, $-(CH_2)_sNR_2$ or $-O(CH_2)_p$halo;

R^c is independently selected from H, halo, OR, or $–C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^1 is selected from $-(CH_2)_sOR$, $-(CH_2)_sNR_2$, $-(CH_2)_s[O(R^c{}_2)_p]_x-R^c$, or $-(CH_2)_s$halo;

R^2 is independently selected from H, OR, CN, halo or -C_{1-6}alkyl, where said alkyl is optionally substituted with one to three groups from –C_{1-6}alkyl, OR^a or halo;

R^3 is independently selected from –C_{1-6}alkyl, heteroaryl or heterocyclyl, wherein said alkyl, heteroaryl or heterocyclyl is optionally substituted with one to three groups from OR^a or R^b;

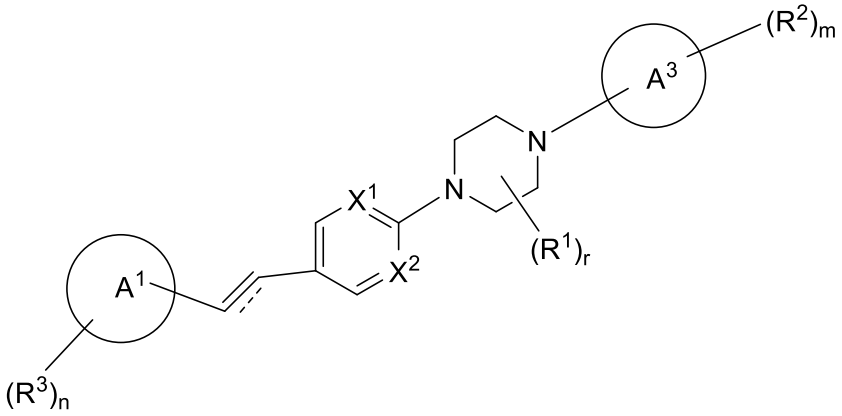
Ring A^1 is selected from pyridinyl, imidazo-pyrimidinyl, triazinyl, pyrimidinyl, imidazo-pyridinyl, pyrazinyl or pyridazinyl;

Ring A^2 is selected from pyrimidinyl, pyridinyl, pyrazinyl or phenyl wherein said pyrimidinyl, pyridinyl, pyrazinyl or phenyl is optionally substituted with one to three groups from –C_{1-6}alkyl, OR^a or halo;

Ring A^3 is selected from pyridinyl, pyrazinyl, pyrimidinyl, pyrrolopyrazinyl, triazinyl, indolyl, imidazolyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, 3,4-dihydro-2H-pyrido[3,2,b][1,4]oxazine or phenyl;

m is selected from 0, 1, or 2;
n is selected from 1, 2, or 3;
p is independently selected from 1, 2 or 3;
r is selected from 1, 2 or 3;
s is independently selected from 0, 1, 2, 3, 4, 5 or 6;
t is independently selected from 0, 1, 2, 3, 4, 5 or 6; and
x is independently selected from 1, 2, 3, 4, 5 or 6.

2. The compound of Claim 1, having the structure of Formula IA:



IA

or a pharmaceutically acceptable salt thereof wherein;

-------- may be absent or may represent a bond;

R is independently selected from H or $–C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^a is independently selected from H, $–C_{1-6}$alkyl, $-(CH_2)_pOR$, $-(CH_2)_p$halo, or $-(CH_2)_pO(CH_2)_p$halo;

R^b is independently selected from H, $–C_{1-6}$alkyl, heterocyclyl, heteroaryl, $-(CH_2)_pOR$, -CN, $-(CH_2)_t$halo, $-(CH_2)_sNR_2$ or $-O(CH_2)_p$halo;

R^c is independently selected from H, halo, OR, or $–C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^1 is selected $-(CH_2)_sOR$, $-(CH_2)_sNR_2$, $-(CH_2)_s[O(R^c{}_2)_p]_x-R^c$ or $-(CH_2)_s$halo;

R^2 is independently selected from H, OR, CN, halo or $-C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^3 is independently selected from $-C_{1-6}$alkyl, heteroaryl or heterocyclyl, wherein said alkyl, heteroaryl or heterocyclyl is optionally substituted with one to three groups from OR^a or R^b;

X^1 is N or CH;

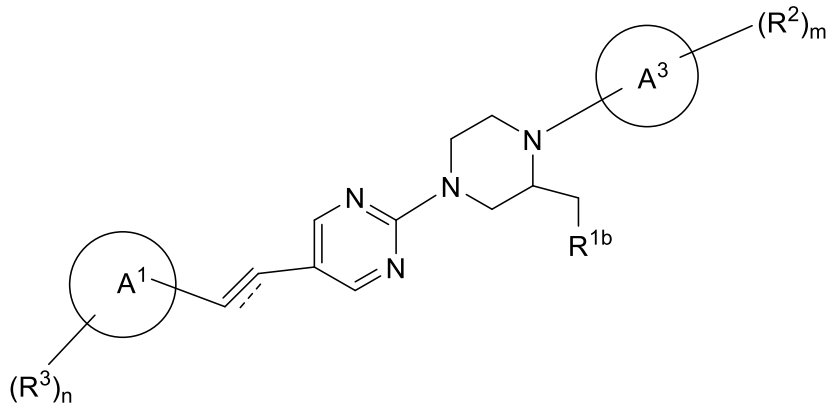
X^2 is N or CH;

Ring A^1 is selected from pyridinyl, imidazo-pyrimidinyl, triazinyl, pyrimidinyl, imidazo-pyridinyl, pyrazinyl or pyridazinyl;

Ring A^3 is selected from pyridinyl, pyrazinyl, pyrimidinyl, pyrrolopyrazinyl, triazinyl, indolyl, imidazolyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, 3,4-dihydro-2H-pyrido[3,2,b][1,4]oxazine or phenyl;

m is selected from 0, 1, or 2;
n is selected from 1, 2, or 3;
p is independently selected from 1, 2 or 3;
r is selected from 1, 2 or 3;
s is independently selected from 0, 1, 2, 3, 4, 5 or 6;
t is independently selected from 0, 1, 2, 3, 4, 5 or 6; and
x is independently selected from 1, 2, 3, 4, 5, or 6.

3. The compound of Claim 1 having the structure Formula IB



IB

or a pharmaceutically acceptable salt thereof wherein;

-------- may be absent or may represent a bond;

R is independently selected from H or $–C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^a is independently selected from H, $–C_{1-6}$alkyl, $-(CH_2)_pOR$, $-(CH_2)_p$halo, or $-(CH_2)_pO(CH_2)_p$halo;

R^b is independently selected from H, $–C_{1-6}$alkyl, heterocyclyl, heteroaryl, $-(CH_2)_pOR$, -CN, $-(CH_2)_t$halo, $-(CH_2)_sNR_2$ or $-O(CH_2)_p$halo;

R^c is independently selected from H, halo, OR, or $–C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^{1b} is selected from $-[O(R^c{}_2)_p]_x-R^c$,OR, NR_2 or halo;

R^2 is independently selected from H, OR, CN, halo or $-C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

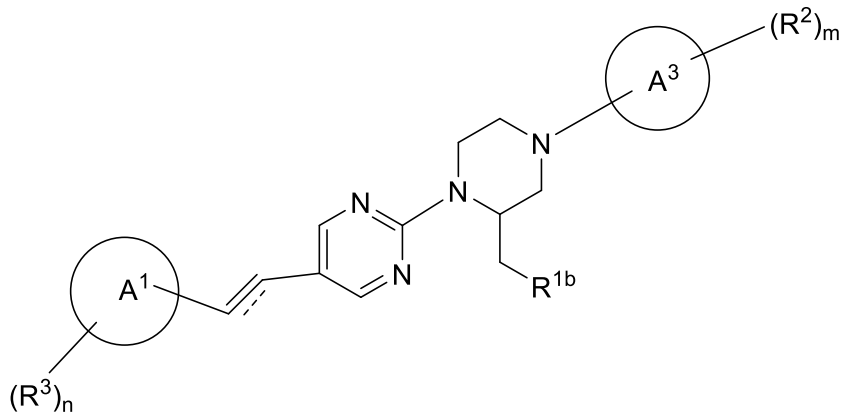
R^3 is independently selected from $–C_{1-6}$alkyl, imidazolyl, morpholinyl, triazolyl, oxazolyl, triazinyl, pyrazolyl, thiazolyl, pyrazinyl, isoxazolyl, azetidinyl, pyrrolidinyl, tetrahydrotriazolopyrazinyl, piperidinyl or pyrimidinyl, wherein said alkyl, imidazolyl, morpholinyl, triazolyl, oxazolyl, triazinyl, pyrazolyl, thiazolyl, pyrazinyl, isoxazolyl, azetidinyl, pyrrolidinyl, tetrahydrotriazolopyrazinyl, piperidinyl or pyrimidinyl is optionally substituted with one to three groups from OR^a or R^b;

Ring A^1 is selected from pyridinyl, imidazo-pyrimidinyl, triazinyl, pyrimidinyl, imidazo-pyridinyl, pyrazinyl or pyridazinyl;

Ring A^3 is selected from pyridinyl, pyrazinyl, pyrimidinyl, pyrrolopyrazinyl, triazinyl, indolyl, imidazolyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, 3,4-dihydro-2H-pyrido[3,2,b][1,4]oxazine or phenyl;

m is selected from 0, 1, or 2;
n is selected from 1, 2, or 3;
p is independently selected from 1, 2 or 3;
s is independently selected from 0, 1, 2, 3, or 4;
t is independently selected from 0, 1, 2, 3, 4, 5 or 6; and
x is independently selected from 1, 2, 3, 4, 5 or 6.

4. The compound of Claim 1, having the structure of Formula IC



IC

or a pharmaceutically acceptable salt thereof wherein;

-------- may be absent or may represent a bond;

R is independently selected from H or $–C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^a is independently selected from H, $–C_{1-6}$alkyl, heterocyclyl, heteroaryl, $-(CH_2)_pOR$, $-(CH_2)_p$halo, or $-(CH_2)_pO(CH_2)_p$halo;

R^b is independently selected from H, $–C_{1-6}$alkyl, $-(CH_2)_pOR$, -CN, $-(CH_2)_t$halo, $-(CH_2)_sNR_2$ or

-$O(CH_2)_p$halo;

R^c is independently selected from H, halo, OR, or $–C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^{1b} is selected from $-[O(R^c{}_2)_p]_x-R^c$, OR, NR_2 or halo;

R^2 is independently selected from H, OR, CN, halo or $-C_{1-6}$alkyl, where said alkyl is optionally substituted with one to three groups from $–C_{1-6}$alkyl, OR^a or halo;

R^3 is independently selected from $–C_{1-6}$alkyl, imidazolyl, morpholinyl, triazolyl, oxazolyl, triazinyl, pyrazolyl, thiazolyl, pyrazinyl, isoxazolyl, azetidinyl, pyrrolidinyl, tetrahydrotriazolopyrazinyl, piperidinyl or pyrimidinyl, wherein said alkyl, imidazolyl, morpholinyl, triazolyl, oxazolyl, triazinyl, pyrazolyl, thiazolyl, pyrazinyl, isoxazolyl, azetidinyl, pyrrolidinyl, tetrahydrotriazolopyrazinyl, piperidinyl or pyrimidinyl is optionally substituted with one to three groups from OR^a or R^b;

Ring A^1 is selected from pyridinyl, imidazo-pyrimidinyl, triazinyl, pyrimidinyl, imidazo-pyridinyl, pyrazinyl or pyridazinyl;

Ring A^3 is selected from pyridinyl, pyrazinyl, pyrimidinyl, pyrrolopyrazinyl, triazinyl, indolyl, imidazolyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, 3,4-dihydro-2H-pyrido[3,2,b][1,4]oxazine or phenyl;

m is selected from 0, 1, or 2;
n is selected from 1, 2, or 3;
p is independently selected from 1, 2 or 3;
s is independently selected from 0, 1, 2, 3, or 4;
t is independently selected from 0, 1, 2, 3, 4, 5 or 6; and
x is independently selected from 0, 1, 2, 3, 4, 5 or 6.

5. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A^1 is selected from pyrimidinyl or pyridinyl;

Ring A^3 is selected from pyridinyl, pyrazinyl, pyrimidinyl, or triazinyl;

m is selected from 0 or 1; and
n is selected from 1 or 2.

6. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A^1 is pyridinyl or pyrimidinyl.

7. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A^2 is pyrimidinyl.

8. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A^3 is selected from pyridinyl, pyrimidinyl, pyrazinyl or triazinyl.

9. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-(CH_2)_sOR$ or $-(CH_2)_s[O(R^c{}_2)_p]_x-R^c$.

10. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is independently selected from $-C_{1-6}$alkyl, imidazolyl, morpholinyl, triazolyl, oxazolyl, triazinyl, pyrazolyl, or isoxazolyl, wherein said alkyl, imidazolyl, morpholinyl, triazolyl, oxazolyl, triazinyl, pyrazolyl, or isoxazolyl is optionally substituted with one to three groups from OR^a or R^b.

11. A compound selected from

Ex No.	**Chemical Name**
1	(*R,E*)-(4-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-1-(pyrimidin-2-yl)piperazin-2-yl)methanol;

Ex No.	Chemical Name
2	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
3	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
4	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(3-((fluoromethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
5	(*R,E*)-5-(2-(6-(4H-1,2,4-triazol-4-yl)pyridin-3-yl)vinyl)-2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidine;
6	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-((2-methoxyethoxy)methyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidine;
7	(*R,E*)-(2-(4-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)methanol;
8	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(5-(fluoromethyl)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine;
9	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-(methoxymethyl)-4-(5-(methoxymethyl)pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
10	(R)-(4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-1-(pyrimidin-2-yl)piperazin-2-yl)methanol;
11	(R)-5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
12	(R)-5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)-2-(4-(6-fluoropyrimidin-4-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine;
13	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(6-fluoropyrimidin-4-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine;
14	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(6-chloropyrimidin-4-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine;
15	(*R,E*)-(1-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-4-(6-fluoropyrimidin-4-yl)piperazin-2-yl)methanol;

Ex No.	Chemical Name
16	(*R,E*)-4-(5-(2-(2-(4-(4-fluoropyridin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)morpholine;
17	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(4-fluoropyridin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine;
18	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidine;
19	(*R,E*)-6-(2-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)-2-methylimidazo[1,2-a]pyrimidine;
20	(*R,E*)-2-(5-(2-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole;
21	(*R,E*)-7-(4-(5-(2-(6-(1H-pyrazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrrolo[1,2-a]pyrazine;
22	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(3-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidine;
23	(*R,E*)-(1-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-4-(pyrazin-2-yl)piperazin-2-yl)methanol;
24	(*R,E*)-(1-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-4-(pyrimidin-4-yl)piperazin-2-yl)methanol;
25	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-(methoxymethyl)-4-(5-methylpyrimidin-2-yl)piperazin-1-yl)pyrimidine;
26	(*R,E*)-5-(5-(2-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole;
27	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(5-fluoropyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine;
28	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;
29	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(2-fluoropyridin-4-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine;
30	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine;

Ex No.	Chemical Name
31	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(2-((2-fluoroethoxy)methyl)-4-(pyridin-4-yl)piperazin-1-yl)pyrimidine;
32	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(6-fluoropyridin-3-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine;
33	(*R,E*)-(1-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-4-(6-fluoropyridin-3-yl)piperazin-2-yl)methanol;
34	(*R,E*)-4-(4-(5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-2-fluoropyrimidine; and
35	(*R,E*)-5-(2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)-2-(4-(5-(2-fluoroethoxy)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine;
36	(R,E)-5-(5-(2-(2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole
37	(R,E)-5-(2-(6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-3-yl)vinyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine
38	(R,E)-5-(5-(2-(2-(3-((2-(2-fluoroethoxy)ethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole
39	1-((2-((R)-4-(5-((E)-2-(6-(1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)-3-fluoropropan-2-ol
40	(R,E)-2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-(2-(6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl)vinyl)pyrimidine
41	(R,E)-5-(5-(2-(2-(3-((2-fluoroethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole
42	(R,E)-5-(5-(2-(2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-4-yl)piperazin-1-yl)pyrimidin-5-yl)vinyl)pyridin-2-yl)oxazole
43	(R,E)-2-(2-((2-fluoroethoxy)methyl)-4-(5-(2-(2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)vinyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
44	(R)-2-(2-((2-fluoroethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
45	(R)-5-((6-(4H-1,2,4-triazol-4-yl)pyridin-3-yl)ethynyl)-2-(4-(6-fluoropyrimidin-4-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine

Ex No.	Chemical Name
46	(R)-2-(4-(5-((2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
47	(R)-2-(4-(5-((6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
48	(R)-5-(5-((2-(3-((2-(2-fluoroethoxy)ethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)oxazole
49	(R)-2-(2-((2-fluoroethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-3-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
50	(R)-2-(2-((2-fluoroethoxy)methyl)-4-(5-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
51	(R)-2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine
52	(R)-2-(3-((2-(2-fluoroethoxy)ethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine
53	(R)-2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-4-yl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine
54	(R)-2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-5-((2-(3-(methoxymethyl)-4-(pyrimidin-4-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyrimidine
55	(R)-5-(5-((2-(3-((2-fluoroethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)oxazole
56	(R)-2-(4-(5-((2-(1-(fluoromethyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
57	(R)-2-(4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)-6-fluoropyrazin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine
58	(R)-5-((6-(4H-1,2,4-triazol-4-yl)pyridin-3-yl)ethynyl)-4-fluoro-2-(3-(methoxymethyl)-4-(pyrimidin-4-yl)piperazin-1-yl)pyrimidine
59	(R)-5-((6-(3-fluoro-4H-1,2,4-triazol-4-yl)pyridin-3-yl)ethynyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine
60	(R)-2-(4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-4-fluoropyrimidine

Ex No.	Chemical Name
61	(R)-4-(4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-2-fluoropyrimidine
62	(S)-5-(5-((2-(3-((2-fluoroethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)oxazole
63	3-(((R)-4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-1-(pyrimidin-2-yl)piperazin-2-yl)methoxy)-2-fluoropropan-1-ol
64	(R)-5-(5-((2-(4-(2-fluoropyridin-4-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)oxazole
65	1-(4-(6-fluoropyrimidin-4-yl)-1-(5-((6-(oxazol-5-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)piperazin-2-yl)-N-methylmethanamine
66	(R)-5-(5-((2-(4-(5-(2-fluoroethoxy)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)oxazole
67	1-fluoro-3-(((R)-4-(5-((6-(oxazol-5-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-1-(1,3,5-triazin-2-yl)piperazin-2-yl)methoxy)propan-2-ol
68	(R)-5-((6-(3-fluoroazetidin-1-yl)pyridin-3-yl)ethynyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine
69	(R)-5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)-2-(4-(6-fluoropyrazin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine
70	(R)-2-(4-(5-((6-(4H-1,2,4-triazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-((2-fluoroethoxy)methyl)piperazin-1-yl)-1,3,5-triazine
71	(R)-5-((6-(4H-1,2,4-triazol-4-yl)pyridin-3-yl)ethynyl)-2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine
72	5-((6-((S)-3-fluoropyrrolidin-1-yl)pyridin-3-yl)ethynyl)-2-((R)-3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine
73	(R)-1-(5-((2-(3-((2-fluoroethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-1H-pyrazol-4-amine
74	(R)-5-(5-((2-(3-((3-fluoropropoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)oxazole
75	(R)-7-(5-((2-(3-((2-fluoroethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyridin-2-yl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine

Ex No.	Chemical Name
76	(R)-5-((6-(4-(2H-1,2,3-triazol-2-yl)piperidin-1-yl)pyridin-3-yl)ethynyl)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine
77	(R)-2-(4-(5-((6-(1-(2-(2-fluoroethoxy)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
78	(R)-2-(2-((2-(2-fluoroethoxy)ethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
79	(R)-5-((2-(3-((2-(2-fluoroethoxy)ethoxy)methyl)-4-(1,3,5-triazin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)-2,5'-bipyrimidine
80	(R)-2-(4-(5-((6-(1H-imidazol-1-yl)pyridin-3-yl)ethynyl)-4-fluoropyrimidin-2-yl)-2-((2-methoxyethoxy)methyl)piperazin-1-yl)-1,3,5-triazine
81	(R)-2-(4-(5-((6-(6-fluoropyrimidin-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine-5-carbonitrile
82	(R)-2-(3-((2-(2-(2-fluoroethoxy)ethoxy)ethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine
83	(R)-2-(3-(13-fluoro-2,5,8,11-tetraoxatridecyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine
84	(R)-2-(4-(5-((2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
85	(R)-2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-5-((2-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyrimidine
86	(S)-5-((2-(4H-1,2,4-triazol-4-yl)pyrimidin-5-yl)ethynyl)-2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidine
87	(S)-2-(4-(5-((2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-3-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
88	(R)-5-fluoro-2-(4-(5-((2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine
89	(R)-5-((2-(4H-1,2,4-triazol-4-yl)pyrimidin-5-yl)ethynyl)-2-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidine
90	(R)-5-fluoro-2-(4-(5-((6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)pyrimidine

Ex No.	Chemical Name
91	(R)-2-(4-(5-((2-(1-(3-fluoropropyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)-2-(methoxymethyl)piperazin-1-yl)-1,3,5-triazine
92	(R)-5-(2-fluoroethoxy)-2-(2-(methoxymethyl)-4-(5-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)pyrimidine
93	(R)-5-(5-((2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)oxazole
94	(R)-2-(4-(6-fluoropyrimidin-4-yl)-3-(methoxymethyl)piperazin-1-yl)-5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidine
95	(R)-2-(2-((fluoromethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
96	(S)-2-(3-((2-fluoroethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine
97	(R)-5-fluoro-2-(2-((2-fluoroethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-3-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)pyrimidine
98	(R)-2-(2-((2-fluoroethoxy)methyl)-4-(5-((2-(1-methyl-1H-pyrazol-5-yl)pyrimidin-5-yl)ethynyl)pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazine

or a pharmaceutically acceptable salt thereof.

12. The compound of Claim 11 selected from Ex. No. 1, 2, 3, 4, 12, 13, 17, 29, 31, 32 34, 38, 43, 44, 46, 48, 49, 51 and 52, or a pharmaceutically acceptable salt thereof.

13. The compound of Claim 11 selected from Ex. No. 1, 2, 3, 12, 13, 29, 32, 38, 44, 46 or 52 or a pharmaceutically acceptable salt thereof.

14. The compound of Claim 1 or 11, or a pharmaceutically acceptable salt thereof, which is labeled with an isotope selected from ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I or ^{131}I.

15. The compound of Claim 1 or 11, or a pharmaceutically acceptable salt thereof, which is isotopically labeled with ^{3}H, ^{11}C or ^{18}F.

16. A pharmaceutical composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutical excipient.

17. A method of measuring the clinical efficacy of therapeutic agents for Parkinson's disease comprising the steps of

a) measuring the amount of alpha-synuclein aggregate formation in a patient's brain tissue after administration of an isotopically-labeled compound of Formula I, according to Claim 14, wherein the patient is one diagnosed with PD and before treatment with said therapeutic agent,

b) measuring the amount of alpha-synuclein aggregate formation in the patient's brain tissue after administration of an isotopically-labeled compound of Formula I, according to Claim 14 and after treatment with said therapeutic agent, and

c) analyzing whether said therapeutic agent stopped or decreased the progression of alpha-synuclein aggregate formation in the patient's brain tissue.

18. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, for use as an imaging agent.

19. A compound of Claim 14, or a pharmaceutically acceptable salt thereof, for use as an imaging agent.